Cost-effectiveness of a potential future Helicobacter pylori vaccine in the Netherlands

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Published in:
Vaccine

DOI:
10.1016/j.vaccine.2008.11.081

Publication date:
2009

Vaccine 27 (2009) 846–852

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of a potential future *Helicobacter pylori* vaccine in the Netherlands: The impact of varying the discount rate for health

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ARTICLE INFO

Article history:
Received 26 September 2008
Received in revised form
18 November 2008
Accepted 22 November 2008
Available online 11 December 2008

Keywords:
Helicobacter pylori
Cost-effectiveness
Discount rate

ABSTRACT

To estimate the cost-effectiveness of a potential *Helicobacter pylori* (HP) vaccine for the Dutch situation, we developed a Markov model. Several HP prevalence scenarios were assessed. Additionally, we assessed the impact of the discount rate for health on the outcomes, as this influence can be profound for vaccines. When applying the current discount rate of 1.5% for health, the expected cost-effectiveness of HP vaccination is estimated below the informal Dutch threshold of €20,000/LYG when the HP prevalence is assumed ≥20% in the Dutch population. In conclusion, we showed that HP vaccination could possibly be a cost-effective intervention. However, this depends to a large extend on the prevalence of HP in the population. Furthermore, we showed the large impact of the discount rate for health on the cost-effectiveness of a HP vaccination program, illustrative for other vaccination programs.

1. Introduction

The prevalence of *Helicobacter pylori* (HP) in the Western world has decreased over the last decades, especially in younger birth cohorts [1]. Also, in the Netherlands the prevalence of HP infections in young adults decreased from 23% in 1978 to 11% in 1993 [1]. The overall prevalence of HP in the Netherlands is estimated at 30–50% [2,3]. In developing nations the prevalence of HP infections is probably much higher [4]. Despite this decrease in the Western world, HP is still one of the most common bacterial pathogens in humans.

Infection with HP is associated with several clinical complications, including gastritis, peptic ulcer disease, gastric cancer, and mucosa-associated lymphoid tissue (MALT) lymphoma. This association is clearly described for gastritis and peptic ulcer disease, in which eradication of HP often cures the condition [5]. Although for gastric cancer and MALT lymphoma the association was mainly based on retrospective epidemiologic research [6], the results of these studies had such strength that the working group of the International Agency for Research on Cancer concluded that infection with HP is a definite cause of cancer in humans [7]. However, hereafter this association between HP infection and gastric cancer has been confirmed in prospective studies such as conducted by Uemura et al. [8,9].

The two most important clinical complications in both numbers and costs are peptic ulcer disease and gastric cancer. In 2003 these two conditions together were responsible for more than 2000 deaths and €122 million of direct medical costs in the Netherlands [10,11]. The exact timeline of the development of these serious complications due to a HP infection is unknown yet. Nevertheless, as it is known that a HP infection is usually acquired in childhood [12], HP vaccination of infants seems to be the only way of preventing these clinical complications as a result of a HP infection. However, no HP vaccine has been marketed yet.

In the development of a HP vaccine a few issues arise. Firstly, HP infection persists even after a vigorous host immune response. A future vaccine must therefore generate a response that differs from a natural response. This can be achieved by generating an even stronger than natural response or a response through other means. Secondly, HP antigens may induce hypersensitivity or autoreactive responses. These two arguments argue against the use of attenuated vaccines or crude whole-cell preparations [13]. Furthermore, HP strains differ markedly. Vaccines under development must therefore focus on antigen(s) which are highly conserved and expressed in vivo. However, the absence of any clear immune correlates of protection makes the development of a appropriate vaccine difficult. Urease, cytotoxin-associated gene antigen (CagA), vacuolating cytotoxin A (VacA) and neutrophil-activating protein (NAP) have been considered as potential vaccine antigens [14]. Potential vaccines which have been examined in clinical trials most often contained recombinant urease [14]. However, efficacy (i.e. immunogenicity) of these vaccines in humans has been disappointing so far [14]. Recently, Mafertheiner et al. focused on a vaccine

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doi:10.1016/j.vaccine.2008.11.081

containing the three conserved antigens: CagA, VacA and NAP [15]. They demonstrated satisfactory safety and immunogenicity of the vaccine, which warrants further clinical research.

Nowadays, as in many other countries, in the Netherlands screening programs are valued with respect to their cost-effectiveness (i.e. cost per life year gained) before implementation. In the Netherlands interventions are certainly considered cost-effective if cost-effectiveness is estimated below a threshold of €20,000 per life year gained [16]. This threshold is informal and certainly not undisputed, but often used by decision makers. One important factor in cost-effectiveness analyses concerning vaccines is the discount rate used. Discounting is a technique that reflects existing time preference: preferring future costs over current costs and current benefits and gains over those in the future. For vaccination programs, benefits are usually gained at a later point in time than the costs are made. For a HP vaccine this is also the case, with the first benefits to be expected at least 20 years after vaccination. In the first Dutch guidelines concerning pharmacoeconomic research, which were introduced in 1999, a discount rate of 4% for money and health outcomes was advocated [17]. In this period it was common practice to use the same discount rate for health and money [18,19]. During recent years this insight has been changed and the committee designing Dutch guidelines on pharmacoeconomic research has introduced a discount rate of 1.5% for health, whereas the discount rate for money remained at 4% [20,21]. For the background on these different discount rates we refer to other papers [21,22].

In this paper we calculate the cost-effectiveness of a potential HP vaccine with respect to preventing peptic ulcer disease and gastric cancer for the Dutch situation. Furthermore, as indicated above, the impact of using different discount rates for health is shown.

2. Data and methods

2.1. Model

We designed a Markov model to estimate the cost-effectiveness of a potential HP vaccine [23]. The Markov model was constructed in TreeAge Data PRO^{tm} 2005 and is shown in Fig. 1. The model consists of six stages to characterize the progression to (i) gastric cancer death due to a HP infection, (ii) peptic ulcer death due to a HP infection and (iii) death due to other causes. We analysed the hypothetical pathway of a cohort of children from birth to 85 years of age. The situation in which the HP vaccination program would be implemented was compared to the current situation of no vaccination.

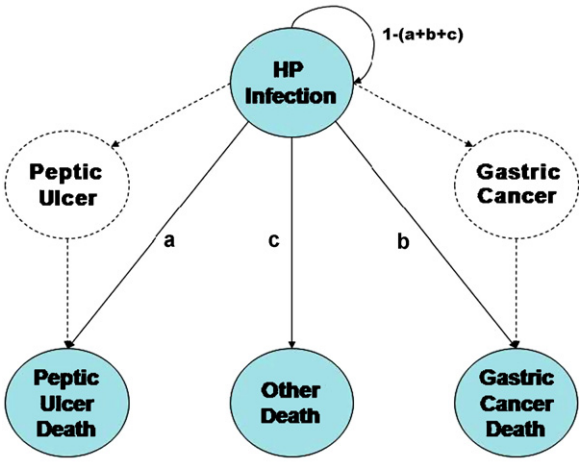

Fig. 1. Markov model of disease progression due to a *Helicobacter pylori* (HP) infection. Markov cycle specific transition probabilities are reflected by a–c. The dashed lines and transparent states indicate that all costs related to peptic ulcer disease and gastric cancer were included although not explicitly modelled.

Transition probabilities "a"–"c" were derived from the number of gastric cancer deaths, peptic ulcer deaths and all deaths reported in 2003 for the Netherlands [10]. Data for 2003 were used to be consistent with other available data (see below). The death rates (r) were converted into probabilities (p) by solving: $p = 1 - e^{-rt}$, where t is the time period [24]. The 5-year transition probabilities are shown in Table 1. We choose a cycle time of 5 years as the number of gastric cancer and peptic ulcer deaths were only available for the 5-year age classes as given in Table 1. For the situation including HP vaccination these probabilities were adjusted using the population attributable risks (PARs) and vaccine efficacy which was assumed at 80% (range: 50–100%). We evaluated several scenarios with different HP prevalences in the population as the prevalence in the Netherlands is estimated at 30–50% but shows a decreasing trend as in most western countries [1]. The exact estimation procedure of the PARs is described in Appendix A. Ergo, the transition probabilities of death due to gastric cancer and peptic ulcer were decreased through the PARs and vaccination effectiveness, while the transition probabilities of death due to other causes were assumed to be equal in both situations.

For our evaluation the Dutch birth cohort of 2003 was followed through the model. This birth cohort consisted of 200,297 children: 102,870 boys and 97,427 girls. We choose a birth cohort as vacci-

Table 1
Transition probabilities for each Markov cycle per 5-year period.

Markov cycle	Age	Peptic ulcer death		Gastric cancer death		Other death	
		Male	Female	Male	Female	Male	Female
1	0–4	0.000000	0.000000	0.000000	0.000000	0.006452	0.004827
2	5–9	0.000000	0.000000	0.000000	0.000000	0.000923	0.000561
3	10–14	0.000000	0.000000	0.000000	0.000000	0.000838	0.000674
4	15–19	0.000000	0.000000	0.000000	0.000000	0.002032	0.001155
5	20–24	0.000010	0.000000	0.000000	0.000021	0.002691	0.001236
6	25–29	0.000000	0.000000	0.000010	0.000020	0.003003	0.001687
7	30–34	0.000008	0.000000	0.000008	0.000023	0.003583	0.001994
8	35–39	0.000007	0.000000	0.000030	0.000031	0.004822	0.003676
9	40–44	0.000031	0.000008	0.000116	0.000103	0.008563	0.006343
10	45–49	0.000000	0.000009	0.000229	0.000078	0.013570	0.011224
11	50–54	0.000035	0.000027	0.000342	0.000217	0.022124	0.016773
12	55–59	0.000048	0.000049	0.000808	0.000273	0.037070	0.024192
13	60–64	0.000129	0.000129	0.001191	0.000465	0.059604	0.035385
14	65–69	0.000288	0.000222	0.001983	0.000711	0.100339	0.056321
15	70–74	0.000427	0.000286	0.003493	0.001239	0.169303	0.094210
16	75–79	0.000870	0.000609	0.004345	0.001973	0.276526	0.163343
17	80–84	0.001194	0.001211	0.006964	0.002741	0.440646	0.288807

Table 2
Gender- and age-specific population costs due to peptic ulcer disease and gastric cancer in the Netherlands in 2003 (million €).

Age	Peptic ulcer		Gastric cancer	
	Male	Female	Male	Female
0–4	0	0.1	0	0
5–9	0	0	0	0
10–14	0.2	0	0	0
15–19	0.1	0	0	0
20–24	0.3	0.1	0	0
25–29	0.4	0.2	0	0
30–34	0.8	0.3	0.1	0.2
35–39	1	0.5	0.4	0.3
40–44	1.7	0.7	0.6	0.5
45–49	1.4	0.9	0.9	0.8
50–54	2.2	1.3	1.8	1.1
55–59	2.6	1.5	3.2	1.6
60–64	2.6	1.3	4	1.9
65–69	3.5	2.6	5.1	2.4
70–74	4.6	4.9	5.7	2.8
75–79	4.2	7.6	4.9	3.2
80–84	3.6	7.5	3.4	2.8

nation for HP is assumed to be best done in infants. For simplicity, it was assumed that all children were vaccinated (100% coverage). This may be justified by the fact that the vaccination coverage in the Netherlands is high, for the national vaccination program this is approximately 96% [23]. The immunization is assumed to consist of three doses given in the first year of life. So, we assumed that all children were vaccinated after 1 year. Furthermore, we assumed that vaccination in children provided a lifelong protection for HP-associated illness, because both the infection rate in adults is low and a vaccine may give a lifetime protection.

2.2. Costs

Both the costs of vaccination and the direct medical costs associated with gastric cancer and peptic ulcer disease were considered. All costs were reported in €2003. The costs of the vaccine were assumed at €50 per dose [26]. These costs were not discounted as they were made on $t = 0$. Direct medical costs associated with gastric cancer and peptic ulcer disease were available for 2003 [27]. In particular, the total costs for the whole Dutch population due to peptic ulcer disease and gastric cancer were determined at €70.7 million and €51.7 million, respectively [27]. Subsequently these yearly total costs were stratified to gender and 5-year age classes (Table 2). These gender and age-group specific costs were then divided by the total number of gender and age-group specific deaths due to gastric cancer and peptic ulcer disease, respectively. Subsequently these gender and age-group specific 'costs per peptic ulcer death' and 'costs per gastric cancer death' were attached to the accompanying states of the Markov model. Note that both cost estimates include the costs associated with peptic ulcer disease and gastric cancer, respectively, for non-deceased persons as well. For example, if 1 out of 100 persons diagnosed with peptic ulcer dies the 'costs per peptic ulcer death' represents the costs of all these 100 persons, including the 99 patients not being deceased. Accordingly, the economic consequences as a result of HP vaccination are fully taken into account, yet be it crudely in being assigned to deaths only.

2.3. Life years gained (LYG)

In the model the number of life years lived by the 2003 birth cohort was estimated both for the scenarios with and without HP vaccination. As mentioned, in the first case the transition probabilities of death due to gastric cancer and peptic ulcer were decreased through the PARs and vaccination effectiveness. The transition probabilities of death due to other causes were assumed to be equal in both cases. The difference in total number of live years lived between these scenarios was considered to be the total number of LYG by HP vaccination. To study the impact of different discount rates for health outcomes the life years were discounted using the current discount rate of 1.5% as well as the former used discount rate of 4% [16,19,20].

Table 3
Parameter values with the accompanying distributions used in the Markov model.

Input variable	Base case	Distribution	Reference
Birth cohort			
Male	102,870	–	[5]
Female	97,427	–	[5]
Vaccine inputs			
Efficacy % (range)	80 (50–100)	Triangular	[21]
Doses per course	3	–	[21]
Cost per dose	€50	–	[21]
Helicobacter pylori risks[a]			
PAR peptic ulcer range	0.19–0.54	Implicitly defined	[24,25]
PAR gastric cancer range	0.13–0.43	Implicitly defined	[24,25]

PAR, population attributable risk.
[a] Several *Helicobacter pylori* prevalence scenarios (10%, 20%, 30%, 40% and 50%) were evaluated. See Appendix A for details.

2.4. Cost-effectiveness analysis

The incremental cost-effectiveness of HP vaccination compared to the current situation without HP vaccination was estimated in terms of costs per LYG. To evaluate the level of uncertainty in the outcomes a probabilistic sensitivity analysis was undertaken with probability distributions for vaccine efficacy and the PARs [28]. The model input parameter values together with the associated distributions are given in Table 3. As no information on vaccine effectiveness was available, we used the estimates given by the manufacturers as previously reported by Rupnow et al. [26]. Vaccine effectiveness was assumed to follow a triangular distribution.

The distribution for the PARs is implicitly defined as for the natural logarithm of the RR (LnRR), which was used to construct the PARs (see Appendix A), the normal distribution may be assumed to apply [29,30]. As mentioned above to evaluate the level of uncertainty associated with the HP prevalence we analysed several prevalence scenarios (10%, 20%, 30%, 40% and 50%). For each scenario we conducted 10,000 Monte Carlo simulations [28]. These results were subsequently presented in cost-effectiveness acceptability curves [31,32]. In the Netherlands, for cost-effectiveness decision makers use an informal threshold of €20,000/LYG (i.e. prevention programs are certainly considered cost-effective when cost-effectiveness is estimated below €20,000/LYG) [33].

As we are still a long way from the registration of an effective HP vaccine that can have prophylactic use in humans, the exact efficacy that such a vaccine will have is still very uncertain [14]. Therefore, to fully evaluate the impact of the vaccine efficacy on the outcomes an univariate sensitivity analysis was performed on this parameter [28]. In this univariate sensitivity analysis we estimated the cost-effectiveness for a vaccine efficacy of 50% as well as 100% for all HP prevalence scenarios.

3. Results

Table 4 presents the results of the expected value analysis for both discount rates for health. The estimated total vaccination costs incurred by the hypothetical cohort are shown together with the averted costs and LYG when compared to the current situation without HP vaccination. It is shown that the incremental cost-effectiveness ratio decreases when the HP prevalence increases.

Table 4
Expected value analysis comparing *Helicobacter pylori* (HP) vaccination with the current situation of no vaccination presented for a 4% discount rate and a 1.5% discount rate for health.

Discount rate	HP prevalence	Total LYG	Vaccination costs (million €)	Total costs prevented (million €)	ICER (€/LYG)
4%	0.1	145	30.04	1.18	198,704
	0.2	256	30.04	2.03	109,347
	0.3	341	30.04	2.67	80,288
	0.4	411	30.04	3.18	65,447
	0.5	467	30.04	3.58	56,667
1.5%	0.1	810	30.04	1.18	35,632
	0.2	1420	30.04	2.03	19,722
	0.3	1899	30.04	2.67	14,417
	0.4	2283	30.04	3.18	11,769
	0.5	2598	30.04	3.58	10,183

Shaded cells reflect scenarios where cost-effectiveness is estimated below the informal Dutch threshold of €20,000/LYG.
LYG, life years gained.
ICER, incremental cost-effectiveness ratio.

When applying the current discount rate of 1.5% for health, the cost-effectiveness of HP vaccination is estimated below the informal Dutch threshold of €20,000/LYG when the HP prevalence is assumed ≥20% in the Dutch population. However, when applying the former 4% discount rate even with a HP prevalence of 50% HP vaccination is still estimated potentially not cost-effective (incremental cost-effectiveness: €57,000/LYG).

The results of the Monte Carlo simulations for the different HP prevalence scenarios are given in Table 5. The median together with the 95th percentiles are presented for both discount rates. The probability that HP vaccination is cost-effective (<€20,000/LYG) is estimated below 0.5 for all five HP prevalence scenarios when a discount rate of 4% is applied. However, when using the current discount rate of 1.5% HP vaccination is estimated cost-effective with a probability of more than 0.95 when the HP prevalence is assumed ≥30% in the Dutch population. The accompanying cost-effectiveness acceptability curves for a discount rate of 1.5% and 4% for health are depicted in Figs. 2 and 3, respectively.

The influence of the vaccine efficacy on the cost-effectiveness is shown in Fig. 4. When vaccine efficacy is increased to 100% the incremental cost-effectiveness ratio is decreased by approximately 25% for both health discount rates and all HP prevalence scenarios. Note that here a decrease in incremental cost-effectiveness is in favour of HP vaccination. The incremental cost-effectiveness ratio is on the other hand increased by approximately 58% compared to the baseline analysis (i.e. vaccine efficacy = 80%) when vaccine efficacy is assumed at 50%. Furthermore, the effect of a change in efficacy is only slightly increased if HP prevalence is increased.

4. Discussion

In this study, we estimated the cost-effectiveness of a potential HP vaccine. Although we are still far from developing a HP vaccine that can have prophylactic uses in humans, we evaluated the possible economic consequences of HP vaccination [15]. Here, we only took the preventive effect on peptic ulcer and gastric cancer into account. Furthermore, we assessed the influence of the discount rate for health on the results. We specifically compared the outcomes using a 4% discount rate with using a 1.5% discount rate as recently this discount rate has been changed from 4% to 1.5% in the Dutch guidelines for pharmacoeconomic research [17,20].

According to the current Dutch guidelines and informal cost-effectiveness threshold (€20,000/LYG) this study reveals that a HP vaccine has the potential to be cost-effective for the Dutch situation when the HP prevalence is 20% or more. When the HP prevalence equals or exceeds 30% the probability of being cost-effective is estimated to be even >0.95.

As the development of a HP vaccine is still in progress only a few cost-effectiveness studies have been published so far [26]. Rupnow et al. conducted a cost-effectiveness analysis on HP vaccination for the US [26]. They estimated that, if future health benefits and costs are discounted at 3% as recommended for the US, a HP vaccine could be cost-saving. As in this paper, they included the disease burdens from peptic ulcer and gastric cancer only [26].

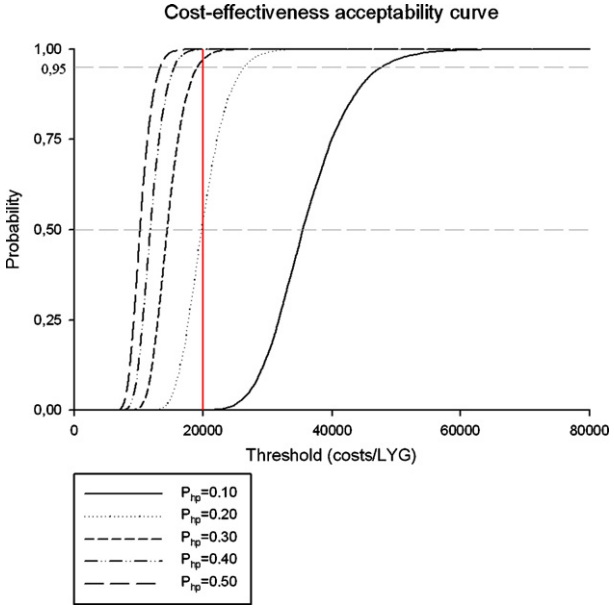

Fig. 2. Cost-effectiveness acceptability curves for the five different *Helicobacter pylori* prevalence scenarios using a 1.5% discount rate health; probability of being cost-effective for a given cost-effectiveness threshold. The red vertical line represents the informal Dutch threshold of €20,000/LYG. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Table 5
Results of the probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations.

	Median (€/LYG)		95th percentile (€/LYG)	
HP prevalence	Rate: 4%[a]	Rate: 1.5%[a]	Rate: 4%[a]	Rate: 1.5%[a]
0.1	198,614	35,479	266,578	47,770
0.2	110,307	19,774	145,292	26,367
0.3	80,658	14,482	106,217	19,143
0.4	65,939	11,837	85,948	15,564
0.5	57,066	10,259	74,338	13,391

Shaded cells reflect scenarios where cost-effectiveness is estimated below the informal Dutch threshold of €20,000/LYG LYG, life years gained.
[a]Discount rate for health.

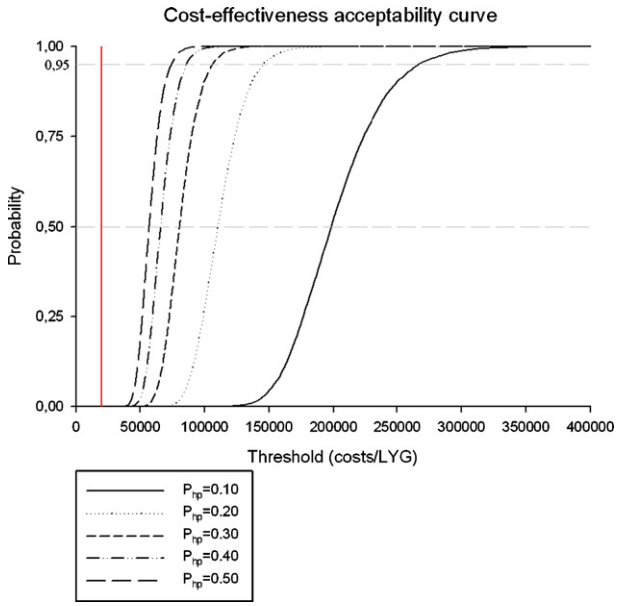

Fig. 3. Cost-effectiveness acceptability curves for the five different *Helicobacter pylori* prevalence scenarios using a 4% discount rate for health; probability of being cost-effective for a given cost-effectiveness threshold. The red vertical line represents the informal Dutch threshold of €20,000/LYG. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

There are several limitations of our study. Pharmacoeconomic analyses, in general, prefer the cost per quality adjusted life year (QALY) as the main outcome measure. However, as there were no data available on the decrease in quality of life due to peptic ulcer disease or gastric cancer it was not possible to provide reliable estimates of QALYs. In economic evaluations the costs per QALY are in general more favourable in terms of cost-effectiveness than the costs per LYG.

As there were no Dutch data available on the incidence of both peptic ulcer disease and gastric cancer, we calculated the 'costs per peptic ulcer death' and the 'costs per gastric cancer death' by dividing the total costs by the number of deaths. This probably resulted in a conservative estimation of the cost-effectiveness as there were costs associated with age-categories where no deaths were reported (e.g. males aged 10–14 years suffering from peptic ulcer disease). These costs, which could potentially also be averted by vaccination, were not included in the analysis. Also, the pragmatic choice of assigning costs to deaths may involve an actual shift of some those costs years into the future. Given the procedure of discounting this consequently involves a potential underestimation of those costs and again renders a conservative estimate of cost-effectiveness. Furthermore, we did not take any costs related to the set-up of an universal HP vaccination program into account. Consequently, the outcomes are not influenced by the coverage as all the direct medical costs currently considered in this analysis are directly related to the number of people being vaccinated.

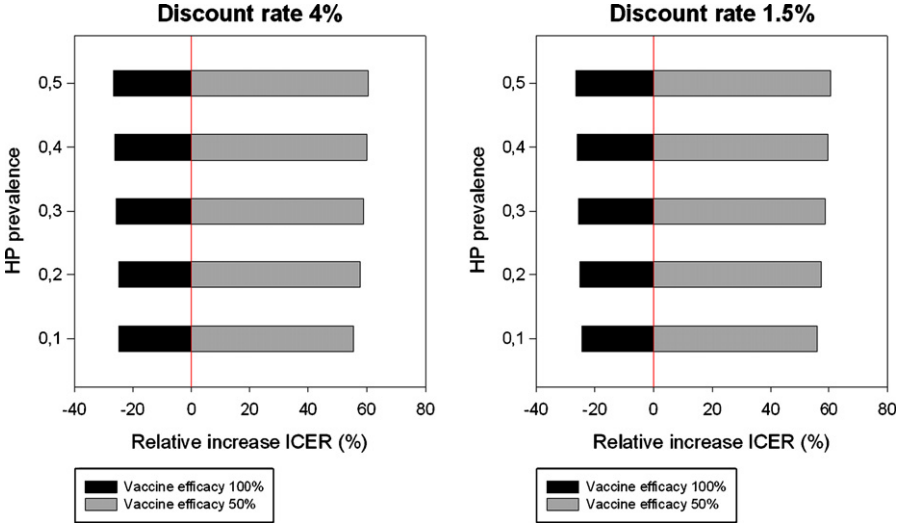

Fig. 4. Univariate sensitivity analyses on vaccine efficacy for the five different *Helicobacter pylori* (HP) prevalence scenarios using a 4% and 1.5% discount rate for health. The vertical red line at $x = 0$ indicates the expected cost-effectiveness for the different scenarios, where vaccine efficacy was assumed at 80%. ICER = incremental cost-effectiveness ratio. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Furthermore, the possible effects of HP vaccination on gastritis and the relative rare disease MALT lymphoma were not modelled in this analysis. Whereas the causal relationship between HP and gastritis is clearly confirmed [5], there are strong believes that this relationship also exists for MALT lymphoma [6]. So, inclusion of both disease states in the Markov model is likely to lead to a more favourable cost-effectiveness of HP vaccination as both diseases, and associated costs and decreases in quality of life, could possibly also be prevented by vaccination. Furthermore, as no HP vaccine is currently available there are still a lot of uncertainties associated with the parameter values used in the model. For example, only crude estimates for vaccine effectiveness can be used. However, we took these uncertainties into account in both a probabilistic and deterministic sensitivity analysis. Finally, the exact HP prevalence in the Netherlands is unknown [1–3]. However, it is known that the prevalence has been declining in western countries the last decades [1]. In general, the cost-effectiveness of vaccination programs largely depends on the incidence of the particular infectious disease in the population. To take this uncertainty related to the HP prevalence and the trend in decrease into account we evaluated several scenarios with a prevalence ranged from 0.1 to 0.5.

As it is likely that the HP incidence will decline further in the next decades, a preventive program aimed at high-risk groups (i.e. high-prevalence groups) may become more feasible than a population-based approach. Previously it has been shown that the prevalence in the migrant population in the Netherlands is considerably higher than in the autochthonous population [2,34]. Accordingly, children of immigrants from high-endemic countries may constitute a target group for HP vaccination. With respect to Hepatitis B a specific vaccination program for children of parents from high-Hepatitis B prevalence countries recently has been added to the Dutch national immunization program [35]. Key factors for the success of such a targeted vaccination program would certainly be the coverage rate achieved among these autochthonous populations, the possibility to achieve a relatively low price for the vaccination despite the non-universal setting and an enhancement of general notion that preventive programs are worthwhile investments.

It is clear that preventive programs benefit from a lowering in discount rate [36–39]. In general vaccination and screening programs most often avert diseases which would have occurred in the (far) future. Ergo, while the monetary investments need to be made now the benefits are only gained later in time. In this study these beneficial effects of a change in discount rate are clearly shown. When using the former 4% discount rate, the cost-effectiveness ratios of the different HP prevalence scenarios are consistently much higher compared to the cost-effectiveness ratios when using the new 1.5% discount rate for health. In case of a HP vaccine this relevant beneficial effect of a lower discount rate for health was expected as most of the health benefits are gained after a long period of time. In general, prevention programs might become more increasingly introduced due to the implementation of a lower discount rate for health. In this example, assuming a HP prevalence of 30%, according to the current Dutch guidelines HP vaccination is considered cost-effective ($p > 0.95$) and should be implemented from a pharmacoeconomic point of view. However, when the former discount rate of 4% is applied HP vaccination is estimated not cost-effective (ICER > €80,000/LYG) and should not be implemented.

As indicated above, the literature is accumulating that health should indeed be discounted at a significantly lower discount rate than money [36,39]. Factors contributing to lower time preference for health than for money are the desire to eliminate dread [40], the increasing value of health over time [36] and the potential double discounting of health effects [41]. Even zero and negative time preferences have been suggested for health. In particular, Van der Pol and Cairns reviewed the literature on empirical assessments of the discount rate, showing that up to 39% of respondents in individual studies expressed negative discount rates and up to 36% expressing no time preference (discount rate of 0%) [40]. In their own empirical study both authors found approximately 20% of persons exhibiting zero or negative time preference [40]. Previously, Loewenstein and Prelec analysed preferences for various sequences of events, also indicating a possible negative rate of time preference [42]. Ergo, consensus seems to come on using lower discount rates for health than for money, down to potentially zero or even negative rates for health. For achieving an adequate valuation of preventive interventions such as vaccination, the issue of zero or negative discounting certainly warrants more research in the near future.

In conclusion, in this paper we showed that HP vaccination could possibly be a cost-effective intervention. However, among other things this depends to a large extend on the prevalence of HP in the population. Although we performed a probabilistic sensitivity analysis on vaccine efficacy and PARs, one should be reserved in drawing conclusions from this study as no HP vaccine has been registered to this moment. Therefore, future research is required to further evaluate the cost-effectiveness of HP vaccination. Furthermore, as there are alternative strategies to decrease the number of complications caused by HP infections (e.g. population-based screening for HP and subsequent treatment [43]), HP vaccination should be compared to those in future economic analyses as well. Finally, we showed the large impact of the discount rate for health on the cost-effectiveness of a HP vaccination program, illustrative for other vaccination programs in the Netherlands.

Acknowledgements

Conflict of interest statement: This study was not sponsored. At the time this study was performed Rogier M. Klok worked at the University of Groningen. Currently he is employed by Wyeth Pharmaceuticals (Hoofddorp, the Netherlands).

Appendix A

The estimation of the population attributable risks (PARs) of a HP infection for both gastric cancer and peptic ulcer disease for the Netherlands is crucial in our analysis. The PAR estimates the proportion of disease (i.e. gastric cancer or peptic ulcer disease) in the study population that is attributable to the exposure (here HP) [30]. The PAR depends on the prevalence of HP infection in the Netherlands, P_{HP}, and the strength of its association (relative risk) with the disease:

$$\mathrm{PAR} = \frac{P_{HP}(\mathrm{RR} - 1)}{1 + P_{HP}(\mathrm{RR} - 1)}$$

with the relative risk (RR) being the ratio of the probability of the disease occurring in the exposed group versus the non-exposed group [30]. The RRs were extracted from two meta-analyses [44,45]. In particular, the RRs for peptic ulcer disease and gastric cancer were estimated at 3.3 (95% C.I.: 2.6–4.4) and 2.5 (95% C.I.: 1.9–3.4), respectively.

Data from adults show a prevalence of HP infection of 30–50% in the Netherlands [2,3]. As yet the prevalence has decreased in most Western countries we calculated the PARs for several scenarios with HP prevalences ranging from 10% to 50% [1]. The estimated Dutch PARs associated with gastric cancer and peptic ulcer disease are shown in Table 6. Accordingly, the proportions of peptic ulcer disease and gastric cancer attributable to a HP infection were estimated at 0.19–0.54 and 0.13–0.43, respectively, depending on the HP prevalence.

Table 6
Population attributable risks (PARs) of a *Helicobacter pylori* (HP) infection for peptic ulcer disease and gastric cancer.

HP prevalence	PAR peptic ulcer (95% C.I.)	PAR gastric cancer (95% C.I.)
0.1	0.19 (0.14–0.25)	0.13 (0.08–0.19)
0.2	0.32 (0.24–0.41)	0.23 (0.15–0.32)
0.3	0.41 (0.32–0.51)	0.31 (0.21–0.42)
0.4	0.48 (0.39–0.58)	0.38 (0.27–0.49)
0.5	0.54 (0.44–0.63)	0.43 (0.31–0.55)

C.I., confidence interval.

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